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EXAMINER

SCHWADRON, R

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1644

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

081700565

Applicant(s)

gruenberg

Examiner

Ren Schwadron, Ph.D.

Group Art Unit

1644

--The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address--**Period for Reply**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status Responsive to communication(s) filed on 7/10/2000 and 12/12/2000. This action is **FINAL**. Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.**Disposition of Claims** Claim(s) 1, 4, 6, 8-13, 15, 22-35, 155-217

is/are pending in the application.

 Of the above claim(s) 1, 4, 6, 8-13, 15, 30, 157, 159, 161, 163, 169, 173, 174-217 is/are withdrawn from consideration. Claim(s) _____ is/are allowed. Claim(s) 22-29, 31-35, 155, 156, 158, 160, 162, 164-168, 170-172 is/are rejected. Claim(s) _____ is/are objected to. Claim(s) _____ are subject to restriction or election requirement.**Application Papers** See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. The proposed drawing correction, filed on _____ is approved disapproved. The drawing(s) filed on _____ is/are objected to by the Examiner. The specification is objected to by the Examiner. The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119 (a)-(d)** Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d). All Some* None of the CERTIFIED copies of the priority documents have been received. received in Application No. (Series Code/Serial Number) _____. received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____.

Attachment(s) Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ Interview Summary, PTO-413 Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152 Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____**Office Action Summary**

1. Regarding applicants comments in the amendment filed 7/10/2000, it appears that the Examiner erroneously withdrew the elected species (claims 155-173) as per the amendment filed 10/21/99. Therefore, claims 155-173 will now be examined along with claims 22-29,31-35. Regarding claims 155-173, in the amendment filed 5/27/98, claim 159 was erroneously numbered claim 160. Said claim has been renumbered as 159, and the claims following said claim have also been renumbered. Claims 157,159,161,163,169,173 are drawn to nonelected species. Claim 157 is drawn to a method that does not use exogenous cytokines as per nonelected claim 1. Claim 159 is drawn to CD4+ T cells (the elected species is Th1). Claim 161 is drawn to CD8+ T cells (the elected species is Th1). Claim 163 is drawn to Th2 cells (the elected species is Th1). Claims 169 and 173 recite mixtures containing Th2 and Th3 cells (the elected species is Th1). Regarding claims 211-217 they are drawn to a nonelected species of method (method does not use IL-2 as per nonelected claim 1). Regarding applicants comments, it would require an undue burden for the Examiner to search the ever growing number of different species of methods present in the instant application. Regarding applicants comments, in the event that the elected species was determined free of the prior art, then further specie(s) would be examined until prior art is found. If no prior art was found, all species would be examined. The requirement is still deemed proper and is therefore made FINAL.
2. Claims 157,159,161,163,169,173 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, the requirement having been traversed in Paper No. 24.
3. Claims 22-29,31-35,155,156,158,160,162,164-168,170-172, are under consideration.

RESPONSE TO APPLICANTS ARGUMENTS

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-29,31-35,155,156,158,160,162,164-168,170-172 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "treating the cells to induce differentiation of mononuclear cells into regulatory T cells". There is support for a limitation of the scope of original claim 22. There is no support in the specification as originally filed for the scope of the claimed invention (eg. the claimed invention constitutes new matter).

There is no support in the specification as originally filed for the recitation of "homogenous population" in claim 22. There is no support in the specification as originally filed for the scope of the claimed invention (eg. the claimed invention constitutes new matter).

6. Claims 22-29,31-35,155,156,158,160,162,164-168,170-172 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive

Claims 22 and 155 are indefinite in the recitation of "regulatory T lymphoid cells" because it is unclear what this means or encompasses. Claim 155 is also indefinite in the recitation of "have the ability to control or direct an immune response, but do not act directly as effector cells". The specification on page 19 discloses that "a regulatory immune cell is any mononuclear cell with a defined cytokine production profile in which such cytokine profile does not directly mediate an effector function" and that said cell "has the ability to control or direct an immune response, but does not act as an effector cell in the response". However, it is unclear what this means or encompasses. While the specification discloses that Th1 or Th2 are "regulatory immune

cells", the art recognizes that said cells are effector cells with regards to the pathogenesis of a variety of different autoimmune diseases (see Liblau et al., pages 34-38). For example, Liblau et al. teach that Th1 cells are involved in the pathogenesis of IDDM wherein said cells bind islet antigens via TCR mediated antigen specific recognition of said islet antigens (see page 35, first column penultimate paragraph). Liblau et al. teach that the lymphokines secreted by said cells are involved in the pathogenesis of IDDM. Thus, according to the definition in the specification Th1, Th2 or Th3 are not "regulatory immune cells" because they function as effector cells and the cytokines they produce also function in a variety of different effector mechanisms. It is unclear as to what cell population is encompassed by this term and it is unclear what the aforementioned definition actually means.

Regarding applicants comments, applicant states that according to the specification that "regulatory" versus "effector" cells can be distinguished by the ability of effector cells to "directly eliminate pathogens or tumor cells" (amendment filed 5/27/98, page 28). However, Mosmann et al. (Immunology Today, 1996) teach that Th1 (a form of regulatory cell as defined in the specification) secrete lymphotoxin (see Table 1), wherein the art recognizes that lymphotoxin is directly cytotoxic to viruses and tumor cells (see Arai et al., columns 1 and 2). Thus, said Th1 can directly eliminate pathogens or tumor cells via secretion of lymphotoxin. Therefore, it is unclear as what "regulatory" cell means or encompasses because while applicant argues that "regulatory" versus "effector" cells can be distinguished by the ability of effector cells to "directly eliminate pathogens or tumor cells", the art recognizes that "regulatory" cells such as TH1 also can directly eliminate pathogens or tumor cells. Thus it is unclear as to what distinguishes a regulatory T cell from an effector T cell. Regarding applicants comments about the specification, page 20, lines 23-26, said definition does not disclose that "directly eliminate pathogens or tumor cells" excludes lymphotoxin mediated cytotoxic mechanisms. Furthermore, said passage also includes reference to B cells wherein B cells do not kill target cells by a cell contact mediated mechanism (eg. they secrete a cytotoxic molecule (eg. antibody)).

7. Regarding priority for the claimed inventions with regards to the application of prior art, the claimed inventions are not disclosed in parent application provisional application 60/044693 (the application formerly known as 08/506668), and therefore priority with regards to the application of prior art is taken as the filing date of PCT WO 97/052349 to which applicant claims

priority. For example, there is no disclosure in 60/044693 of the method of claim 22 or 155 for generating "regulatory T lymphoid cells" per se (60/044693 refers to methods of generating autologous effector T lymphoid cells). Regarding applicants comments, there is no disclosure in parent application provisional application 60/044693 of the term "regulatory T lymphoid cells" or a method of producing such cells. There is no disclosure in 60/044693 of the method of claim 22, parts b and c.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 22-28,34,155,156,158,160,162,164,167,168,170-172 are rejected under 35 U.S.C. 102(e) as being anticipated by Babbitt et al. (US Patent 5,766,920).

While it is unclear what the terms referred to in paragraph 6 of this Office Action mean or encompass, for the purposes of application of prior art the claimed methods will be interpreted as methods wherein Th1 cells are expanded and subsequently administered. Babbitt et al. teach methods for producing Th1 cells, wherein patient mononuclear cells are removed and expanded in vitro (see columns 5 and 6) and used for autologous cell therapy (see abstract). The method taught by Babbitt et al. uses IFN γ enriched supernatants and OKT3 (eg. antiCD3 antibody) to produce Th1 populations (see columns 5 and 6). Babbitt et al. teach that autologous expanded Th1 cells are reinfused to treat autoimmune disease (see column 2, first complete paragraph). The cells are expanded to clinically relevant numbers (see column 19). The cells are treated with two or more activating proteins specific for cell surface proteins found on the Th1 (eg. T3CS (see column 5)). The cells are purified from the material (see column 8, penultimate paragraph). The cells can be specific for a particular antigen (see claim 12). Babbitt et al. teach expansion to 10^9 cells and infusion of said cells into a patient (see column 19, penultimate paragraph) wherein said number of cells is encompassed by "about 10^{10} cells". Babbitt et al. teach that the cells grown at a final concentration of 10^7 cells/ml and that 10^9 cells were administered (eg. the 10^9 cells would have

been present in 100 mls of media, see column 19, penultimate paragraph). Babbitt et al. teach that the cell population produced is at least 75% Th1 (eg. said population could be homogenous).

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 22-28,33,34,35,155,156,158,160,162,164,166,167,168,170-172 are rejected under 35 U.S.C. § 103 as being unpatentable over Babbitt et al. (US Patent 5,766,920) in view of Cracauer et al. (US Patent 4,804,628).

While it is unclear what the terms referred to in paragraph 6 of this Office Action mean or encompass, for the purposes of application of prior art the claimed methods will be interpreted as methods wherein Th1 cells are expanded and subsequently administered. Babbitt et al. teach methods for producing Th1 cells, wherein patient mononuclear cells are removed and expanded in vitro (see columns 5 and 6) and used for autologous cell therapy (see abstract). The method taught by Babbitt et al. uses IFN γ enriched supernatants and OKT3 (eg. antiCD3 antibody) to produce Th1 populations (see columns 5 and 6). Babbitt et al. teach that autologous expanded Th1 cells are reinfused to treat autoimmune disease (see column 2, first complete paragraph). The cells are expanded to clinically relevant numbers (see column 19). The cells are treated with two or more activating proteins specific for cell surface proteins found on the Th1 (eg. T3CS (see column 5)). The cells are purified from the material (see column 8, penultimate paragraph). The cells can be specific for a particular antigen (see claim 12). Babbitt et al. teach expansion to 10^9 cells and infusion of said cells into a patient (see column 19, penultimate paragraph) wherein said number of cells is encompassed by "about 10^{10} cells". Babbitt et al. teach that the cells grown at a final concentration of 10^7 cells/ml and that 10^9 cells were administered (eg. the 10^9 cells would have been present in 100 mls of media, see column 19, penultimate paragraph). Babbitt et al. do not teach the use of a hollow fiber bioreactor in said method. Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro (see columns 1-3). It would have been prima facie obvious to one of

ordinary skill in the art at the time the invention was made to have created the claimed invention because Babbitt et al. teach the claimed method except for the use of a hollow fiber bioreactor and Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro. A routinéer would have grown larger numbers of cells than 10^9 in order to obtain larger numbers of cells in order to ascertain the optimal dosage to use to obtain the desired clinical effect in any particular type of treated disease. One of ordinary skill in the art would have been motivated to do the aforementioned because Cracauer et al. teach that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in culture." (column 1).

12. Claims 22-29, 31, 34, 155, 156, 158, 160, 162, 164, 167, 168, 170-172 are rejected under 35 U.S.C. § 103 as being unpatentable Babbitt et al. (US Patent 5,766,920) in view of Garra et al.

While it is unclear what the terms referred to in paragraph 6 of this Office Action mean or encompass, for the purposes of application of prior art the claimed methods will be interpreted as methods wherein Th1 cells are expanded and subsequently administered. Babbitt et al. teach methods for producing Th1 cells, wherein patient mononuclear cells are removed and expanded in vitro (see columns 5 and 6) and used for autologous cell therapy (see abstract). The method taught by Babbitt et al. uses IFN γ enriched supernatants and OKT3 (eg. antiCD3 antibody) to produce Th1 populations (see columns 5 and 6). Babbitt et al. teach that autologous expanded Th1 cells are reinfused to treat autoimmune disease (see column 2, first complete paragraph). The cells are expanded to clinically relevant numbers (see column 19). The cells are treated with two or more activating proteins specific for cell surface proteins found on the Th1 (eg. T3CS (see column 5)). The cells are purified from the material (see column 8, penultimate paragraph). The cells can be specific for a particular antigen (see claim 12). Babbitt et al. teach expansion to 10^9 cells and infusion of said cells into a patient (see column 19, penultimate paragraph) wherein said number of cells is encompassed by "about 10^{10} cells". Babbitt et al. teach that the cells grown at a final concentration of 10^7 cells/ml and that 10^9 cells were administered (eg. the 10^9 cells would have been present in 100 mls of media, see column 19, penultimate paragraph). Babbitt et al. do not teach use of anti-IL-4 antibody in said method. O'Garra et al. teach that anti-IL-4 antibody treatment of CD4+ cells favors the development of Th1 (see page 460, first column). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made to have created the claimed invention because Babbitt et al. disclose a method that produces Th1 cells, while O'Garra et al. teach that anti-IL-4 antibody treatment of CD4+ cells favors the development of Th1 (see page 460, first column). One of ordinary skill in the art would have been motivated to do the aforementioned because O'Garra et al. teach that anti-IL-4 antibody treatment of CD4+ cells favors the development of Th1.

13. Claims 32,164,165 are rejected under 35 U.S.C. 103(a) as being unpatentable over Babbitt et al. (US Patent 5,766,920) in view of Garra et al. as applied to claims 22-29,31,34,155,156,158,160,162,164,167,168,170-172 above, and further in view of June et al. ((WO 94/29436) or (US Patent 5,858,358).

The previous rejection renders obvious the claimed invention except for the limitation of claims 32,164 and 165. June et al. teach that T cells can be expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 (see abstract of either publication). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except for the limitation of claims 32,164 and 165, while June et al. teach that T cells can be expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28. One of ordinary skill in the art would have been motivated to do the aforementioned because Th1 are a subset of T cells and June et al. teach that T cells can be expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28.

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The

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examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.


RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
February 11, 2001